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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2307E-8511PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US98/15717	International filing date *(day/month/year)* 29 JULY 1998	Priority date *(day/month/year)* 30 JULY 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): G01N 33/50, 33/566; C12N 5/10; C07K 14/435, 14/705 and US Cl.: 435/7.2, 7.6, 21		
Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22 FEBRUARY 1999	25 OCTOBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CLAIRE M. KAUFMAN Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (January 1994)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/15717

I. Basis of the report

1. This report has been drawn on the basis of (*Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments*):

[X] the international application as originally filed.

[X] the description, pages 1-47 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-38 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-4 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
comprises a signal transduction assay, use of recombinant RDGC or GPCR, use of a sample comprising whole cells or *in vivo* methods.

ZUCKER teaches a method of measuring membrane potential changes in intact *Drosophila* photoreceptor cells (Figure 3) and calcium changes in *Drosophila* transgenic for a particular rhodopsin (Figure 4). Also taught (page 575, middle of third full paragraph) is that "Furthermore, the genetic dissection of this [phototransduction] pathway in humans and flies has provided fundamental insight into the molecular and cellular basis of inherited retinal disorders...." Also (paragraph bridging columns 1-2 of page 575), "It is here where the study of phototransduction in *Drosophila* offers unprecedented versatility. The study of this signal cascade in the fruit fly *Drosophila melanogaster* makes it possible to use powerful molecular genetic techniques to identify novel transduction molecules and then to examine the function of these molecules *in vivo*, in their normal cellular and organismal environment."

ZUCKER ET AL. (DATABASE GENBANK ON STN, ACCESSION NUMBER M17718) is the nucleic acid sequence of rhodopsin from *Drosophila*.

It would have been obvious to the artisan of ordinary skill to practice the methods of BYK ET AL., substituting recombinant rhodopsin and RDGC for native proteins because the encoding nucleic acids were known several years prior to the methods of BYK ET AL., recombinant production of proteins was well known in the art, and ZUCKER showed that transgenic *Drosophila* could be made which expressed particular rhodopsin pathway proteins. It additionally would have been obvious to transform isolated cells, particularly insect cells, with expression vectors encoding these two proteins since BYK ET AL. had shown that they were involved in the phototransduction signal cascade, expression of proteins in insect cells was well known and routine in the art, and it would have been desirable to use an isolated system in which the presence of particular pathway components could be controlled and the expressed proteins would be in an environment similar to normal cellular environment (*i.e.*, in an insect cell). The advantages of the ability to dissect pathways molecularly were discussed by ZUCKER. To most closely mimic a natural environment, it would have been desirable and obvious to use whole cells in the method of BYK ET AL. instead of membrane preparations because ZUCKER shows that light and calcium applied to whole cells can be used as methods of screening compounds which might influence the phototransduction pathway (*e.g.*, Figure 3).

Claims 1-38 meet the criteria set out in PCT Article 33(4), because they have industrial utility for identification of compounds which modulate RDGC GPCR activity.

---------- NEW CITATIONS ----------
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	2, 5, 8-11, 15-36 and 38	YES
	Claims	1, 3, 4, 6, 7, 12-14, 37	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-38	NO
Industrial Applicability (IA)	Claims	1-38	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 3, 4, 6, 7, 12-14 and 37 lack novelty under PCT Article 33(2) as being anticipated by BYK ET AL.

BYK ET AL. teaches a method of screening *in vitro* for modulators of signal transduction of rhodopsin, a G protein-coupled receptor (GPCR). The method comprises providing a first sample of eye membranes from wild-type and a second sample from RDGC mutant *Drosophila* eyes, contacting the sample with a compound (*e.g.*, calcium or arrestin) suspected of having the ability to modulate RDGC GPCR phosphatase activity, and detecting RDGC GPCR phosphatase activity by means of a phosphorylation assay conducted by measuring mobility on an electrophoretic gel (Figures 2 and 5 and page 1909, paragraph beginning "Arrestin Binding..."). Also taught are eye membranes comprising a GPCR and RDGC phosphatase with GPCR phosphatase activity which are necessarily in a container (page 1908, second paragraph). Note that instructions have no weight in novelty determination.

Claims 1-38 lack an inventive step under PCT Article 33(3) as being obvious over BYK ET AL., ZUCKER and ZUCKER ET AL. (DATABASE GENBANK ON STN, ACCESSION NUMBER M17718).

BYK ET AL. teaches a method of screening *in vitro* for modulators of signal transduction of rhodopsin, a G protein-coupled receptor (GPCR). The method comprises providing a first sample of eye membranes from wild-type and a second sample from RDGC mutant *Drosophila* eyes, contacting the sample with a compound (*e.g.*, calcium or arrestin) suspected of having the ability to modulate RDGC GPCR phosphatase activity, and detecting RDGC GPCR phosphatase activity by means of a phosphorylation assay conducted by measuring mobility on an electrophoretic gel (Figures 2 and 5 and page 1909, paragraph beginning "Arrestin Binding..."). Also taught are eye membranes comprising a GPCR and RDGC phosphatase with GPCR phosphatase activity which are necessarily in a container (page 1908, second paragraph). Note that instructions have no weight in novelty determination. A GPCR signal transduction assay measuring GPTase is shown in Figure 6. BYK ET AL. teach the RDGC gene was cloned several years prior (page 1910, last paragraph). BYK ET AL. does not teach the method of screening described above wherein detection (Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 2, 5, 16, 17, 25, 28, 34, 35 and 38 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): the claims recite "recombinant" RDGC phosphatase or GPCR. The definition of "recombinant" in the description on page 17, lines 16-22 indicates that the "recombinant" protein is different from the native protein, but does not say how they differ. As a result, the metes and bounds of the claims are not clear.

Claims 15 and 23 and dependent claims 16-22 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): The claims are drawn to a method of *in vivo* screening comprising contacting a sample with a test compound. It is unclear how the method can be *in vivo* if a sample and not an animal is used.

Claims 24-36 are not supported by the description of the current application because the method requires providing an animal comprising a cell comprising a GPCR and an RDGC phosphatase and detecting RDGC GPCR phosphatase activity in an animal. Since one would naturally expect the animal to have RDGC GPCR phosphatase activity in some cells and the cell recited by the claim is not particularly identified, it would require undue experimentation to determine when the cell of the claim is being modulated. Further, there is nothing in the claim requiring that the activity detected be from or in the cell recited in line 3 of the claim. There are insufficient method steps to practice the claimed method.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/15717

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :G01N 33/50, 33/566; C12N 5/10; C07K 14/435, 14/705
US CL : 435/7.2, 7.6, 21
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.2, 7.6, 21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, EMBASE, CAPLUS, WPIDS
search terms: rdg?, phosphatas?, phosph!phatase?, g protein coupled receptor, gpcr, c zuker, j vinos

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	BYK ET AL., Regulatory arrestin cycle secures the fidelity and maintenance of the fly photoreceptor cell. Proc. Natl. Acad. Sci. USA. March 1993, Vol. 90, pages 1907-1911, see especially Figures 2 and 5.	1, 3, 4, 6, 7, 10-14 --- 2, 5, 8, 9, 15-38
Y	Database Genbank on STN. US National Library of Medicine (Bethesda, MD USA). GenBank Accession Number M17718. D. melanogaster opsin (Rh3) gene, complete cds. 15 March 1989, see entire document.	5, 17, 28, 35
Y	STEELE ET AL. Drosophila retinal degeneration C (rdgC) encodes a novel serine/threonin protein phosphatase. Cell. 15 May 1992, Vol. 69, pages 669-675, especially Figure 4 and page 674.	1-38

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
19 OCTOBER 1998	30 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CLAIRE M. KAUFMAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/15717

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZUCKER C.S. The biology of vision of drosophila. Proc. Natl. Acad. Sci. USA. 23 January 1996, Vol. 93, No. 2, pages 571-576, see especially page 575 and Figure 1.	1-38
Y	STEELE ET AL. The drosophila rdgC protein phosphatase and protein phosphorylation/dephosphorylation events in vision. Adv. Protein. Phosphatases. 1993, Vol. 7, pages 515-527, see entire document.	1-38
Y, P	VINOS ET AL. A G protein-coupled receptor phosphatase required for rhodopsin function. Science. 01 August 1997, Vol. 277, pages 687-690, see entire document.	1-38
X	PITCHER ET AL. The G-protein-coupled receptor phosphatase: A protein phosphatase type 2A with a distinct subcellular distribution and substrate specificity. Proc. Natl. Acad. Sci. USA. August 1995, Vol. 92, pages 8343-8347, see entire document.	1, 3, 6, 10, 12, 13